New and experimental skin-directed therapies for cutaneous lymphomas

Farkas, A ; Kemeny, L ; French, L E ; Dummer, R

Abstract: Primary cutaneous lymphomas (CLs) originate in the skin and should be differentiated from secondary skin infiltrates, which are manifestations of lymphomas of nodal or extranodal origin. These rare diseases include various lymphoproliferative disorders: cutaneous T-cell lymphomas, cutaneous B-cell lymphomas and some rare subtypes. As definitive cure is often not possible, it is important to control the disease and alleviate symptoms. Patients with early-stage disease limited to the skin usually require skin-directed therapies using topical agents including corticosteroids, chemotherapeutic drugs, bexarotene gel, electron beam therapy and phototherapy. Each of these are effective; however, all have some disadvantages and are associated with significant adverse events. In the field of skin-directed therapies there are interesting developments using antineoplastic compounds, the retinoid tazarotene, imiquimod, gene therapy products (adenovirus vector expressing gamma-interferon), the monoclonal anti-CD20 antibody rituximab, photodynamic therapy and 308-nm excimer laser to mention a few. This review highlights some of the promising new and experimental local therapies for primary CLs and focuses on their efficacy and side effects.

DOI: https://doi.org/10.1159/000241302

Review

Skin Pharmacology and Physiology

Skin Pharmacol Physiol 2009;22:322–334
DOI: 10.1159/000241302

Received: March 17, 2009
Accepted after revision: July 17, 2009
Published online: September 25, 2009

New and Experimental Skin-Directed Therapies for Cutaneous Lymphomas

Arpad Farkas[a] Lajos Kemeny[a] Lars E. French[b] Reinhard Dummer[b]

[a]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary;
[b]Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

Key Words
Skin-directed therapy · Cutaneous lymphoma · Hexadecylphosphocholine · Methotrexate · Tazarotene · Imiquimod · TG-1042 · Rituximab · Photodynamic therapy · 308-nm excimer laser

Abstract
Primary cutaneous lymphomas (CLs) originate in the skin and should be differentiated from secondary skin infiltrates, which are manifestations of lymphomas of nodal or extranodal origin. These rare diseases include various lymphoproliferative disorders: cutaneous T-cell lymphomas, cutaneous B-cell lymphomas and some rare subtypes. As definitive cure is often not possible, it is important to control the disease and alleviate symptoms. Patients with early-stage disease limited to the skin usually require skin-directed therapies using topical agents including corticosteroids, chemotherapeutic drugs, bexarotene gel, electron beam therapy and phototherapy. Each of these are effective; however, all have some disadvantages and are associated with significant adverse events. In the field of skin-directed therapies there are interesting developments using antineoplastic compounds, the retinoid tazarotene, imiquimod, gene therapy products (adenovirus vector expressing γ-interferon), the monoclonal anti-CD20 antibody rituximab, photodynamic therapy and 308-nm excimer laser to mention a few. This review highlights some of the promising new and experimental local therapies for primary CLs and focuses on their efficacy and side effects.

Introduction

Cutaneous lymphomas (CLs) are the second most common non-Hodgkin lymphomas with an estimated annual incidence of 1 new case per 100,000 inhabitants [1]. Primary CLs by definition arise in the skin, while secondary CLs are manifestations of disseminated, primary nodal or extranodal lymphomas [2]. Primary CLs include a broad spectrum of clinically and histologically heterogeneous lymphoproliferative diseases with diverse pathogeneses and clinical manifestations. Around 80% of primary CLs are T-cell types (CTCL), 10–20% are B-cell types (CBCL), and the remaining number of CLs corresponds to rare entities, such as CD4+/CD56+ haematodermic lymphomas, deriving from type 2 dendritic cells. The diagnostic approach includes clinical, histological, immunohistochemical, imaging, haematological and molecular examinations [3].

Classification

The latest classification system presented by the World Health Organization (WHO) and by the European Organization for Research and Treatment of Cancer is compatible with the WHO classification for haematopoietic and lymphoid neoplasias, includes additional entities and respects the organ-specific features of primary CLs [4, 5]. This consensus classification system divides CLs into 3 groups: CTCL and cutaneous natural killer cell lympho-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1660–5527/09/0226–0322$26.00/0

Accessible online at:
www.karger.com/spp

Arpad Farkas, MD, PhD
Department of Dermatology and Allergology, University of Szeged
HU–6720 Szeged (Hungary)
Tel. +36 62 545 259, Fax +36 62 545 954
E-Mail farkas@mail.derma.szote.u-szeged.hu

Table 1. WHO-EORTC classification of CLs

CTCL and cutaneous NK cell lymphomas
MF
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukaemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary peripheral CTCL, unspecified
Primary aggressive epidermotropic CD8+ CTCL (provisional)
γ/δ CTCL (provisional)
Primary CD4+ small/medium-sized pleomorphic CTCL (provisional)
CBCL
Primary marginal zone CBCL
Primary cutaneous follicle centre lymphoma
Primary diffuse large CBCL, leg type
Primary diffuse large CBCL, other
Intravascular large B-cell lymphoma
Precursor haematological neoplasm
CD4+/CD56+ haematodermic neoplasm
(blastic NK cell lymphoma)

EORTC = European Organization for Research and Treatment of Cancer; NK = natural killer.

Table 2. Classical topical treatment options in CL

Skin involvement	Topical therapy
Limited/localized	Corticosteroids
	Nitrogen mustard
	Carmustine
	Local radiation
	Topical retinoid (bexarotene)
	Ultraviolet B
	Psoralen + ultraviolet A
Generalized	Corticosteroids
	Mechlorethamine
	Carmustine
	Ultraviolet B
	Narrow-band ultraviolet B
	Psoralen + ultraviolet A
	Total skin electron beam therapy

mas, CBCL and precursor haematological neoplasms (table 1). Based on the different biological behaviour, CLs may be grouped into prognostic categories such as prelymphomatous 'abortive' disorders, definite malignant lymphomas of low-grade malignancy and definite malignant lymphomas of high-grade malignancy [3].

Skin-Directed Therapies

It is recommended to identify the clinicopathological entity as given both in the classification system and the prognostic category to provide essential information on the behaviour of CLs and to allow the planning of the therapeutic strategy. The recommended approach for treatment is to aim for disease control, since definitive cure is usually not possible. Classical therapeutic modalities can be divided into topical or systemic. Table 2 shows a brief summary of the various standard topical treatment options, which have been reviewed earlier elsewhere [6]. In more advanced stages, various systemic treatment options such as glucocorticoids, extracorporeal photopheresis, recombinant α-interferon (IFN-α), retinoids, chemotherapeutic agents, bone marrow transplantation, fusion toxin denileukin difitox, histone deacetylase inhibitors, purin nucleoside analogue, monoclonal antibodies, cytokines and vaccines are available. The goal of our present work is to highlight some of the promising new and experimental local therapies of CLs.

Hexadecylphosphocholine

Hexadecylphosphocholine is an antineoplastic drug that inhibits tumour cell growth and might also exert immunoregulatory properties [7, 8].

Dummer et al. [9] treated 24 patients with 6% topical hexadecylphosphocholine (1 drop/10 cm^2 lesion) for 8 weeks. Fifteen suffered from mycosis fungoides (MF), 7 had CBCL and 2 had lymphomatoid papulosis. Of 15 CTCL patients, 12 were evaluable. Two complete remissions (CR), 4 partial remissions (PR) and 1 minor remission were observed. Of 7 CBCL patients, 6 were evaluable. One CR, 3 PR, 1 case of stable disease and 1 case of progressive disease were seen. Both patients with lymphomatoid papulosis had a CR. Histological evaluation demonstrated only a partial clearing of infiltrating lymphocytes in lesions that showed PR or CR clinically. Fifty-six percent of evaluable CL patients (10/18) achieved an objective response rate (PR and CR) [9].

Table 3. Therapeutic approaches for the treatment of CTCL and CBCL with the antineoplastic drug hexadecylphosphocholine

References	Patients enrolled	Patients evaluated	Treatment schedule	Clinical response	Histological clearance	Relapse
Dummer et al. [9]	15 CTCL 7 CBCL	12 6	1st week 1 ×/day, next 7 weeks 2 ×/day, in PR or MR additional 4 weeks	2 CR, 4 PR, 1 MR 1 CR, 3 PR, 1 SD, 1 PD	yes in 5 CR patients, but no decrease in lymphocyte numbers in the deeper dermis	n.a.
Dumontet et al. [10]	12 CTCL	12	1st week 1 ×/day, next 7 weeks 2 ×/day	5 CR, 2 PR, 5 SD	n.a.	none until a median follow-up of 12 months in 2 CR + 1 PR patients; in 3 patients, none between 24 and 54 months

MR = Minor remission; SD = stable disease; PD = progressive disease; n.a. = not applicable.

Dumontet et al. [10] performed a phase II trial to evaluate 6% topical hexadecylphosphocholine solution (2 drops/10 cm^2 lesion) for the treatment of 12 CTCL patients. All patients had received at least 1 prior systemic or topical treatment. The study drug was administered for 8 weeks, once per day during the first week, then twice every day for 7 weeks. Five patients were considered to be in CR, 2 patients had PR and 5 patients had stable disease. The overall response rate was 58% with a median duration of response of 12 months. The main side effects were moderate to mild pruritus or desquamation in 57% and 50% of patients, respectively. No systemic or biological toxicity was observed [10]. These studies have shown that hexadecylphosphocholine is a safe, simple and effective treatment in both untreated and previously treated patients in early patch form CL (table 3).

Methotrexate

Methotrexate (MTX) competitively inhibits dihydrofolate reductase, therefore blocks DNA synthesis and prevents mitosis [11]. Oral or parenteral MTX is approved for the treatment of advanced MF; however, its systemic toxicity has precluded its use in patients with early-stage MF. Topical therapy of early-stage MF with the existing oral or parenteral MTX formulations is ineffective because of the inability of the drug to penetrate the stratum corneum from aqueous solutions [12]. For this reason, MTX-laurocapram was developed, which is a topical hydrophilic gel formulation of MTX (1% wt/wt) with the penetration enhancer laurocapram.

Demierre et al. [13] presented the results of a phase I/II study in 10 patients with early-stage MF who were treated topically with MTX-laurocapram. The gel formulation of the product was applied to the total body surface at daily doses of 12.5 or 25 g/m^2, excluding the genital, perianal areas, nipples, face and skin under the breasts, on an every-other-day basis for 24 consecutive weeks. Of 10 patients, 9 completed the study. At the end of the treatment phase (week 24), 3 patients (33%) had a moderate response, 4 (44%) had a slight response and 2 (22%) had no response to treatment. In summary, a total of 7 (78%) patients demonstrated a slight to moderate response to treatment. Adverse events consisted of local skin reactions of mild severity such as pruritus, rash, burning and dryness. No systemic reactions or clinically significant laboratory abnormalities were observed. Serum levels of MTX, as measured 24–48 h following the topical application, were under the lowest limit of detection in all samples analysed [13].

The results obtained in this study indicate that MTX-laurocapram is safe and well tolerated, and it seems that systemic exposure to the drug is not significant. Despite the relatively low number of patients, efficacy outcomes were positive.

Tazarotene

Retinoids, which are derivatives of vitamin A, modulate the differentiation and proliferation of keratinocytes and lymphocytes. Topical bexarotene in gel form is a synthetic retinoid-X-receptor-selective retinoid, which has

already been approved by the Food and Drug Administration (FDA) for the treatment of refractory IA and IB MF lesions. Tazarotene is a synthetic retinoid in a gel or cream formula, which binds to the retinoic acid receptor β- and γ-subtypes. As the latter is the dominant receptor in the skin, the selective binding capacity of tazarotene eliminates many side effects, which possibly occur when retinoic acid receptor subtypes are generally activated. The FDA has approved tazarotene for the treatment of psoriasis and acne vulgaris.

Apisarnthanarax et al. [14] conducted an open-label pilot study to assess the efficacy and tolerability of 0.1% tazarotene gel in the treatment of early patch or plaque MF lesions limited to less than 20% body surface area. Twenty patients were enrolled, 19 received treatment, and 16 completed at least 4 weeks of topical therapy. Eleven of 19 patients or 58% experienced at least moderate (>50%) global improvement in all index lesions, and 35% of 99 index lesions cleared completely. On the basis of grading of index lesions, mean significant differences were observed after treatment in plaque elevation, scaling and erythema. Only pruritus did not change significantly and remained stable. Of 19 patients, 16 (84%) experienced mild or moderate local skin irritation manifested by peeling, erythema, burning and tenderness that was managed successfully with topical steroids or by reducing the frequency of treatment. Histological evaluations showed reductions in lymphocytic infiltrates and percentage of CD45RO+ lymphocytes, and increases in the percentage of CD8+ lymphocytes during the therapy course.

The rate of irritation was similar or slightly higher than that reported with topical bexarotene gel for MF lesions, but the pilot study with tazarotene included few patients, was non-randomized, had no vehicle control and was susceptible to bias in lesion assessments [14]. Nonetheless, these data suggest that tazarotene 0.1% gel combined with topical corticosteroids may be an effective adjuvant therapy for refractory MF lesions.

Imiquimod

Imiquimod is a topical Toll-like receptor (TLR)-7 and TLR-8 agonist constitutively activating the transcription factor NF-κB, therefore inducing the production of pro-inflammatory cytokines and chemokines including IFN-α, IFN-γ, interleukin-12 and tumour necrosis factor-α. This results in activation of antigen-presenting cells and the mounting of a profound T-helper 1 (Th1) antitumoural cellular immune response [15]. The pro-inflammatory activity of imiquimod can also be correlated with adenosine receptor signalling pathways and receptor-independent reduction of adenylyl cyclase activity [16]. At higher concentrations, imiquimod exerts a pro-apoptotic activity, which is dependent on bcl-2 proteins and involves caspase activation [16]. The cream formulation has been approved for the treatment of external genital and perianal warts, actinic keratoses and primary superficial basal cell carcinoma. As CTCL is dominated by T-helper 2 cytokines, the enhancement of Th1 immune responses has a therapeutic role. So far several case reports and a few pilot studies exist, showing the efficacy of imiquimod in patients with different forms of CTCL such as MF [17–27], CD30+ anaplastic large-cell lymphoma [20, 23, 28], primary cutaneous follicle centre lymphoma [29] and primary CBCLs [23, 25].

In a series of 6 CTCL patients, Deeths et al. [21] observed 50% clinical and histological clearing and a significant improvement in clinical scores. Coors et al. [23] observed CR in more than 50% of their CTCL patients, and additionally they observed a PR in 2 out of 3 CBCL patients; however, the effect of imiquimod seemed to be less potent in CBCL.

Generally, treatment frequencies ranged from once daily to once weekly applications. Time to response was already reached after 2 weeks in some patients, and the duration of remission was between 5 and 45 months.

Previous studies of Urosevic et al. [30] showed that the clinical inflammatory reaction in response to imiquimod was correlated with the IFN-α gene signature and with the number of plasmacytoid dendritic cells in treated lesions, showing that these may have a role in the clinical response to imiquimod.

Imiquimod treatment was generally well tolerated; local irritation and erythema were common, but pruritus, burning, pain, tenderness, infections, ulceration and postinflammatory discolouration occurred in some patients [31]. Severe reactions usually developed in patients on an intensive regimen, which usually resolved within 1–2 days after cessation and could be avoided by less frequent applications [17]. Although absorption into the circulation is less than 1%, in rare cases systemic side effects were observed such as fatigue, fever, myalgia, nervous system impairment and gastro-intestinal symptoms [32].

The case reports cited above and pilot studies demonstrated that imiquimod might be effective in some cases with therapy-resistant lesions of CTCL as well as of CBCL with an acceptable safety profile (table 4).

Table 4. Therapeutic approaches for the treatment of CTCL and CBCL with the immune response modifier imiquimod

References	Patients enrolled	Number of lesions	Fluences	Time to response	Clinical response	Histological response	Relapse
Suchin et al. [17]	1	2 CTCL	1×/day	4 months	2 CR	yes, 1 lesion partly	none in 10 months
Dummer et al. [18]	1	multiple CTCL	1×/day	8 weeks	1 CR	n.a.	none in 12 months
Chong et al. [19]	3	3 CTCL	1×/day	32 weeks	3 PR[1]	n.a.	n.s.
Didona et al. [20]	2	2 CTCL	3×/week	8 months	2 CR	yes, 1 lesion was evaluated	none in 8 months
Deeths et al. [21]	6	23 CTCL	1–3×/week	4 weeks	50%[2]	yes, 3 lesions out of 6[3]	none in 24 months
Ardigo et al. [22]	1	1 CTCL	5×/week	24 weeks	1 CR	yes	none in 6 months
Coors et al. [23]	5 3	9 CTCL 11 CBCL	3–5×/week	8–16 weeks 12–52 weeks	5 CR, 2 PD, 2 NR 8 PR, 3 NR	n.a.	none in 5–45 months none in 19–42 months
Chiam and Chan [24]	1	1 CTCL	3–4×/week	5 months	1 CR	n.a.	none in 6 months
Stravrakoglou et al. [25]	1	multiple FCL	1×/day, then 2–4×/week	2–12 weeks	multiple CR	yes	none in 24 months
Martínez-González et al. [26]	4	11 CTCL	3×/week	3–14 months	11 CR	yes, 3 lesions out of 4[3]	follow-up ongoing
Ariffin and Khorshid [27]	2	1 CTCL	2×/week, then 1×/day	12 weeks	1 CR	n.a.	none in 6 months
Ehst et al. [28]	2	3 CTCL	2–7×/week[4]	6–16 weeks	2 CR	n.a.	patient 1: follow-up ongoing[5] patient 2: none in 4 months

FCL = Follicle centre lymphoma; PD = progressive disease; NR = no response; n.a. = not applicable; n.s. = not stated.
[1] Treated lesions demonstrated a mean decrease in surface area of 8.9%.
[2] The physician's global assessment scale was used to judge overall patient response. No change in 1 patient, slight improvement in 2 patients, moderate improvement in 1 patient, marked improvement in 1 patient and almost clear in 1 patient.
[3] One lesion per patient (index) was chosen for histological evaluation.
[4] Concurrent administration of MTX and imiquimod.
[5] Two lesions were treated in patient 1, one of the lesions healed and never recurred.

TG-1042 Adenovirus Vector

IFN-γ is a cytokine with immunostimulatory, antitumour, antiproliferative and anti-angiogenic properties [33].

Intramuscular [34] recombinant IFN-γ has been investigated for the immunotherapy of CTCL with promising response rates, although severe toxicity was seen [34]. Intratumoural delivery of recombinant IFN-γ has been attempted to overcome systemic side effects [35]; however, the short half-life of the cytokine was a complicating factor.

TG-1042 is a replication-deficient adenovirus vector expressing IFN-γ to target CL lesions [36]. Intralesional injection produces sustained local IFN-γ protein levels while systemic IFN-γ levels remain low.

In a phase I/II study, all the 5 evaluable CBCL patients presented with a local response (3 CR and 2 PR), and 45% of the 29 evaluable CTCL patients responded to TG-1042 treatment (7 CR and 6 PR). Out of the total 18 patients with objective local response, 15 showed systemic response with the additional clearance of non-injected skin lesions (7 CR and 8 PR in non-treated tumours). CTCL subtypes, such as MF, Sézary syndrome and CD30+ anaplastic large-cell lymphoma, showed different response rates to TG-1042 injections. Clinical response was seen in 8 out of 20 MF patients, but patients with Sézary syndrome did not benefit from treatment. All 3 evaluable patients with CD30+ anaplastic large-cell lymphoma responded with a CR in the treated lesions. It seems that more localized lesions in earlier stages of the disease in conjunction with CD30 expression respond better to treatment. In general, CBCL lesions are easily accessible

Table 5. Therapeutic approaches for the treatment of CTCL and CBCL with a replication-deficient adenovirus vector expressing IFN-γ (TG-1042)

Reference	Patients enrolled	Patients evaluated	Treatment schedule	Local response	Global response	Histological clearance	Relapse
Urosevic [37]	32 CTCL 6 CBCL	29 5	3×10^{11} TVP TG-1042 i.t. for up to 4 cycles	7 CR, 6 PR 3 CR, 2 PR	15	n.s.	n.s.

TVP = Total viral particles; i.t. = intratumourally; n.s. = not stated.

for treatment and responded very well to TG-1042; therefore, a larger multicentre phase II study currently evaluates the response rates in different CBCL subtypes [37].

Based on a recent work of Urosevic et al. [38], it appears that both the expression of the transgene and the adenoviral vector itself contribute to the regression of skin lesions. Gene expression profiles of skin lesions obtained from CL patients before and after treatment with TG-1042 revealed a distinct gene signature consisting of IFN-γ- and numerous IFN-α-inducible genes. IFN-γ very likely promotes the immunogenicity of the tumour, while type I IFNs, on the other hand, exhibit profound antitumoural effects by acting on host immune cells [38].

Treatment with TG-1042 was well tolerated, usually with grade 1 or 2 adverse events such as injection site reactions, flu-like syndrome, fatigue and possibly dose-dependent headache. Unspecified colitis, vomiting following vasovagal syncope and transient fever were reported as possibly related side effects.

This therapy induced regression in CTCL and CBCL patients both at the injection site and systemically with tolerable side effects (table 5).

Rituximab

Tumoural pre-B and mature B cells express the CD20 antigen, which can be targeted by rituximab, a human-mouse chimeric monoclonal antibody. Rituximab kills CD20+ tumour cells by directly inducing apoptosis, by triggering complement-mediated lysis and by antibody-dependent cell-mediated cytotoxicity [39, 40].

Nodal B-cell lymphoma can be successfully treated with intravenous rituximab infusion as monotherapy or in combination with other agents [41–43].

Heinzerling et al. [44] reported for the first time the use of intralesional rituximab in 2 patients with primary CBCL. One patient had progressive nodular lesions on the scalp and on the face. The other patient presented with recurrence of tumour nodules in different body parts. Rituximab was injected 3 times a week, each time 30 mg, followed by a 3-week treatment-free period. An inflammatory response in the injected lesions was observed approximately 2–3 h after each injection and lasted for a few hours. After 6–9 injections, some of the nodules flattened and diminished in size, and others, including some that were not treated, had completely resolved. No adverse effects occurred except pain during or shortly after injection and, in 1 patient, a slight rise in body temperature. Due to the treatment, a prolonged complete disappearance of B cells from peripheral blood samples was observed [44].

Later on Kerl et al. [45] treated 8 primary CBCL patients with rituximab. Patients selected for treatment had follicle centre (4 patients) and marginal zone (4 patients) lymphoma. These are the most frequent CBCL entities, which have an indolent course and rarely disseminate to internal organs, but their incidence of recurrence is high [5, 46]. Six patients received intralesionally 10–30 mg rituximab, 3 times weekly for 1 or 2 cycles with a 4-week interval. Two patients were treated with intravenous rituximab and received 375 mg/m^2, once weekly for 4 consecutive weeks. All patients reached CR, and the 2 patients treated intravenously did not relapse during a follow-up period of 18–24 months. Four of 6 patients treated intralesionally presented a relapse of new lesions at another site within a mean of 6 months after treatment. However, the injected lesions did not recur. New lesions also responded to another cycle of intralesional rituximab [45].

Intralesional rituximab therapy was well tolerated without severe side effects. All patients reported moderate pain during the injection procedure. On the other hand, no burning or erythema was reported.

Table 6. Therapeutic approaches for the treatment of CBCL with the human-mouse chimeric monoclonal antibody rituximab

References	Patients enrolled	Treatment schedule	Time to response	Clinical response	Histological response	Relapse
Heinzerling et al. [44]	2	30 mg i.l. 3 × /week, 1 week treatment, 3-week treatment-free period	6–9 injections	CR, PR (numbers n.s.)	no (only 2 lesions assessed)	in 12 months 1 new lesion, otherwise n.s.
Kerl et al. [45]	6	10–30 mg i.l. 3 × /week for 1 or 2 cycles with a 4-week interval	CR after 1 or 2 cycles	6 CR	n.s.	4 patients in 4–8 months

i.l. = Intralesionally; n.s. = not stated.

It seems that this treatment has a potential advantage when lesions are localized at sites that are difficult to treat with radiotherapy or surgery and when secondary scarring or alopecia is expected to occur. In summary intralesional rituximab is a valuable alternative option for the treatment of CBCL, but the risk of relapse was relatively high (table 6).

Photodynamic Therapy

Photodynamic therapy (PDT) requires the presence of a photosensitizer, light and oxygen. In dermatology, 5-aminolevulinic acid (5-ALA) and the methyl ester of 5-ALA are the most commonly used photosensitizers, which may semiselectively accumulate in abnormal skin tissue and are converted to protoporphyrin IX, inducing a photochemical and phototoxic skin reaction through reactive oxygen radicals in the presence of visible light [47, 48]. Following serial evaluations immunological effects have been additionally described.

Boehncke et al. showed that the photosensitizer is mainly taken up by the lymphocytes in CL plaques [49] and that PDT has the capability to inhibit proliferation of transformed T cells [50].

Orenstein et al. [51] observed that malignant cells in CTCL plaques have a greater ability to convert ALA into protoporphyrin IX than peripheral blood lymphocytes.

The observations of Rittenhouse-Diakun et al. [52] might explain the greater susceptibility of malignant lymphocytes to photosensitizers. They found that activated lymphocytes express higher levels of CD71 (transferrin receptor), making them able to take up more iron and, therefore, produce more protoporphyrin IX.

Based on several existing reports [51, 53–68], it can be concluded that PDT treatment of CTCL lesions is of benefit in most (CR in more than 86% of cases presented in table 7) but not all patients. The numbers of treatments to reach CR were usually between 1 and 12, and remission periods were between 3 and 106 months (table 7). Lesions in remission had a peculiar histological appearance, since atypical lymphocytes continued to be present in the dermis.

A recent study performed by Mori et al. [69] used ALA-PDT and red light at the standard dose used for basal cell carcinoma to treat 3 patients with single early CBCL lesions. They reported CR following a single session in all of the patients, with a follow-up of between 8 and 17 months.

PDT therapy was tolerated well; in most cases erythema, oedema, postinflammatory hyperpigmentation, local discomfort, burning and pain were reported. In rare cases, superficial blisters, erosion and ulceration occurred.

Based on small studies with few patients and numerous case reports, it seems that CL patients with localized lesions can benefit most from PDT. It is very likely that lymphocytes in the plaque are only inactivated but not eliminated and remission periods are highly variable, therefore a regular follow-up is necessary.

Further studies will be necessary to evaluate whether the combination with other therapeutic modalities enhances efficacy. Umegaki et al. [64] have already reported a case of cutaneous anaplastic large-cell lymphoma, which was effectively treated by PDT prior to radiotherapy.

308-nm Excimer Laser

UVB phototherapy has been used for treating various skin diseases including CL. Different CL forms respond well to either broad-band or narrow-band UVB photo-

Table 7. Therapeutic approaches for the treatment of CTCL with PDT

References	Patients enrolled	Number of lesions	Number of treatments	Clinical response	Histological clearance	Relapse
Svanberg et al. [53]	2	4	1–2	2 CR	n.a.	none in 14 months
Wolf et al. [54]	2	3	4–5	3 CR	yes	none in 3–6 months
Ammann and Hunziker [55]	1	1	1	1 CR	no	n.a.
Stables et al. [56]	1	1	2	1 CR	2/3 of the lesion[1]	none in 12 months
Eich et al. [57]	2	2	8–12	1 CR, 1 PR	yes in CR and PR	in PR after 4 weeks, in CR none in 24 months
Wang et al. [58]	1	3	3	3 CR	n.a.	none in 33 months
Orenstein et al. [51]	2	6	1–2	6 CR	yes	none in 24–27 months
Edstrom et al. [59], Edstrom and Hedblad [60][2]	10	12	2–11	7 CR, 2 PR, 3 NR	yes in CR and PR	in CR, none in 4–21 months (1st follow-up), 71–106 months (2nd follow-up only 4 patients)[3]
Markham et al. [61]	1	1	5	1 CR	yes	none in 12 months
Leman et al. [62]	1	2	2	2 CR	yes	none in 12 months
Paech et al. [63]	1	2	2	2 CR	yes	none in 12 months
Umegaki et al. [64]	1	1	9	1 CR	yes	none in 24 months[4]
Coors and von den Driesch [65]	4	7	1–7	7 CR	n.a.	none in 14–18 months
Zane et al. [66]	5	5	1–9	4 CR, 1 PR	n.a.	none in 12–34 months
Hegyi et al. [67]	1	1	3	1 CR	yes	none in 16 months
Recio et al. [68]	2	2	3	2 CR	yes	none in 24 months

NR = No response; n.a. = not applicable.

[1] Three areas within the lesion were irradiated with 5, 10 and 20 J/cm^2 of white light after 20% topical 5-ALA pretreatment. After 3 months no lymphocytic infiltration was seen in the 2 areas irradiated with 10 and 20 J/cm^2 (2/3 of the lesion).

[2] The original study was published in 2001 [59], and the long-term follow-up was published in 2008 [60].

[3] PDT with topical 5-ALA was combined with radiotherapy for the treatment of cutaneous CD30+ anaplastic large-cell lymphoma.

[4] Following PDT the remaining lesion underwent radiation therapy and a clinically disease-free condition resulted.

therapy. Recently, it has been reported that a 308-nm xenon chloride (XeCl) UVB laser is highly effective for treating psoriasis [70], and, over the past few years, several excimer laser studies have been published for the treatment of early-stage MF.

It seems that effective induction of T-cell apoptosis is responsible for the greater clinical efficacy of XeCl laser compared to other UVB sources [71, 72].

Nistico et al. [73] treated 5 patients with a total of 10 lesions with a clinical and histological diagnosis of primary CL with repeated applications of the XeCl laser, until CR was achieved or up to a maximum of 10 applications. The cumulative UVB dose was between 6 and 12 J/cm^2. After a 1-year follow-up, all patients were in CR [73].

Passeron et al. [74] treated 5 patients with patch-stage or plaque-stage primary CL in a XeCl laser study. The 50 mJ/cm^2 initial fluences were increased by 100 mJ/cm^2 every 2 sessions. Treatment was administered twice weekly until clinical clearance or minimal residual activity was achieved. A CR was obtained for 4 of the 5 patients, and minimal residual activity (PR) was observed in the fifth. Clinical healing was obtained in 11–21 sessions, with a cumulative dose ranging from 2.4 to 16.1 J/cm^2. No clinical recurrence was noted 3 months after the end of the sessions.

Later the same group conducted a XeCl laser trial with 10 MF patients. A total of 29 lesions were treated as described in their previous study. The mean cumulative dose ranged from 1.3 to 16.1 J/cm^2. After treatment sessions, 25 CR and 3 PR were observed, and 1 lesion did not respond. Follow-up was performed in 19 lesions for a median period of 8–26 months; 13 persistent CR, 3 continued PR and in 2 cases relapses were observed, and 1 lesion remained non-responsive. Histology was consistent with clinical results, except for 1 case with persistence of a few mycosis cells in the epidermis despite a clinical appearance of healing [75].

Afterwards this treatment option was studied in lymphomatoid papulosis [76] and CD30+ cutaneous lymphoproliferative disorders [77].

Side effects were manageable; usually slight erythema, pruritic sensation and transient hyperpigmentation were noticed in all patients, with spontaneous resolution. In the case of intense erythema, the sessions were cancelled and the fluence at the next treatment corresponded to the highest dose that did not induce adverse effects.

Table 8 briefly summarizes the results obtained with the 308-nm excimer laser for various CL forms and lymphomatoid papulosis.

Table 8. Therapeutic approaches for the treatment of CTCL and lymphomatoid papulosis with 308-nm excimer laser

References	Patients enrolled	Number of lesions	Sessions	Cumulative UVB dose, J/cm^2	Clinical response	Histological clearance	Relapse
Nistico et al. [73]	5	10	4–10	6–12	10 CR	yes	none in 12 months
Passeron et al. [74]	5	5	11–21	2.4–16.1	4 CR, 1 MR	yes in 3 patients without atypical cells	none in 3 months
Passeron et al. [75]	10	29	6–46	1.3–16.1	25 CR, 3 PR, 1 NR	yes, consistent with clinical response	none in 8–26 months, 19 lesions
Kontos et al. [76]	3	multiple	13–22	0.4–0.5	patient 1: 75% CR[1]; patient 2: 100% CR; patient 3: NR	patient 1: n.a.; patient 2: yes; patient 3: n.a.	in patient 2, none in 13 months

MR = Minor remission; NR = no response; n.a. = not applicable.
[1] Patient 1 had lymphomatoid papulosis, patient 2 and 3 had MF.

Conclusions and Future Perspectives

Skin-directed therapies using topical formulations are preferred for the majority of patients with early-stage CL, which usually include topical corticosteroids, topical chemotherapeutic agents, the topical retinoid bexarotene, electron beam therapy and phototherapy. Not all patients respond to these therapies, and some of them become refractory to treatment [78]. In this field there are interesting developments, but there are often insufficient data to compare the efficacy and side effects of available and possible future therapies.

The topical administration of antineoplastic agents such as MTX is very likely restricted by the poor diffusion of the drug across the stratum corneum. Therefore attempts have been made to increase transdermal transport through electroporation [79, 80] and using an erbium:YAG laser in animal models. Both techniques significantly enhanced the permeation of MTX. The enhancing effect was more pronounced after applying the laser. Electroporation treatment resulted in a twofold increase in MTX flux, laser pretreatment produced a 3- to 80-fold enhancement and combination of laser and electroporation pretreatment resulted in a higher drug permeation than either technique alone [80].

Retinoids have been used for years as monotherapy and in combination for CTCL treatment. Rexinoids have been available since the approval of oral bexarotene for CTCL. Topical retinoids and rexinoids, especially the selective ones, have fewer side effects than the oral ones; therefore, the use of retinoids and rexinoids will require strategies to identify novel receptor-selective subtypes with a better therapeutic index to decrease the possible side effects.

Restoring Th1 immunity in CL is an important therapeutic approach, therefore the role of IFNs (IFN-α and in recent years IFN-γ) and immunomodulators, which are potent IFN inducers, is becoming more important. Imiquimod (TLR-7 and TLR-8 agonist), a potent IFN-α inducer, has been reported to be beneficial for some patients with localized stage IA MF, and agents other than imiquimod are also under investigation. Recent data showed that EAPB0203, a member of the imidazoquinoxaline family, may have a future therapeutic role in the treatment of HTLV-I-negative peripheral T-cell lymphoma [81], and it has also been shown that the novel tellurium immunomodulator AS101 induces a dose-dependent G_2/M arrest in CTCL cell lines and delays tumour growth in mice, when injected intratumourally [82, 83]. Formerly it was shown that a replication-deficient adenovirus, which carries the IFN-γ gene, has a therapeutic effect for the treatment of CL. A phase I/II clinical trial in CTCL and CBCL patients was recently completed, and clinical studies are still ongoing in CBCL patients [36, 37].

The oligonucleotide CpG-7909, which is a TLR-9 agonist, has shown promising results in CTCL patients [84], and a phase I/II study has been initiated to investigate CpG-7909 together with radiation therapy in low-grade B-cell lymphoma or MF patients.

Antibodies against antigens on the surface of lymphoma cells have an emerging therapeutic role. CD20 is

strongly expressed on the surface of malignant B cells and can be targeted by rituximab [39, 40]. In the case of primary CBCLs, intralesional therapy with rituximab has already been found to be effective [44, 45]. In comparison with intravenous administration, intralesional application of the drug allows the use of lower doses and fewer side effects. Recently a clinical study has been designed to investigate the antitumour activity of rituximab combined with CpG-7909 in patients with relapsed/refractory CD20+ B-cell non-Hodgkin's lymphoma [85]. Objective responses occurred in 24% of patients overall and in 50% of patients who after combination therapy received CpG-7909 alone for an additional 20 weeks; this cohort included 2 patients with rituximab-refractory disease. Most common adverse events were mild to moderate systemic flu-like symptoms, injection site reactions and neutropenia [85]. Based on these results, it would be reasonable to check this combination therapy in primary CBCL patients.

Phototherapy has been utilized for decades in the treatment of CL and recently it has been shown that PDT is also an effective, non-invasive and safe therapeutic approach [86]. Reports already exist, which suggest that this therapeutic modality can be effectively used prior to radiotherapy [64]. Treatment of ALA-PDT with PUVA represents a promising option as it was shown that this combination inhibits the proliferation of a lymphoma cell line in vitro [87].

The XeCl laser is a new and very useful form of UVB phototherapy. During XeCl laser therapy, the overall treatment time is shorter, the treatments are less frequent and the cumulative UV dose is significantly lower than those used in standard UV phototherapies; therefore, it is presumed that the lower therapeutic cumulative dose of the XeCl laser involves a lower risk of carcinogenesis. It is considered that longer-wavelength UVB phototherapy would be ideal for the treatment of thick skin lesions, while short-wavelength UVB radiation would be optimal for the treatment of thin ones. To further optimize treatment results, the surface of skin lesions can be moistened to enhance the penetration of radiation. As with other UV therapies, combination therapy seems to be the next step to improve efficacy [88].

Arsenic compounds such as As_2O_3 have been shown to induce cell death by the inhibition of bcl-2. In acute promyelocytic leukaemia, this treatment modality led to CR in 90% of the patients [89–91]. In patients with Sézary syndrome, this kind of therapy has not been successful as As_2O_3 levels were low in the skin [92]. Tun-Kyi et al. [93] have shown that As_2O_3 induced apoptosis of CTCL cells by down-regulating transcription factors that stimulate the expression of anti-apoptotic genes. Local injection of As_2O_3 induced tumour regression in MF tumour-bearing mice [93]. These results demonstrate that As_2O_3 could be a novel local treatment option for CTCL.

In summary, ongoing and future standardized clinical trials will hopefully provide new data regarding experimental skin-directed treatment options for CL patients. As with other already well-established treatment options, combination therapy seems to be a logical future step to improve efficacy.

Acknowledgements

Arpad Farkas is on leave from the Department of Dermatology and Allergology in Szeged, Hungary, and his work was supported by an International Union Against Cancer fellowship.

References

1 Weinstock MA, Gardstein B: Twenty-year trends in the reported incidence of mycosis fungoides and associated mortality. Am J Public Health 1999;89:1240–1244.

2 Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Geerts ML, Goos M, Knobler R, Ralfkiaer E, Santucci M, Smith N, Wechsler J, van Vloten WA, Meijer CJ: EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997;90: 354–371.

3 Burg G, Kempf W, Cozzio A, Dobbeling U, Feit J, Golling P, Michaelis S, Scharer L, Nestle F, Dummer R: Cutaneous malignant lymphomas: update 2006. J Dtsch Dermatol Ges 2006;4:914–933.

4 Burg G, Kempf W, Cozzio A, Feit J, Willemze R, Jaffe ES, Dummer R, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Grange F, Harris NL, Kazakov DV, Kerl H, Kurrer M, Knobler R, Meijer CJ, Pimpinelli N, Ralfkiaer E, Russell-Jones R, Sander C, Santucci M, Sterry W, Swerdlow SH, Vermeer MH, Wechsler J, Whittaker S: WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. J Cutan Pathol 2005; 32:647–674.

5 Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ: WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105: 3768–3785.

6 Kim EJ, Hess S, Richardson SK, Newton S, Showe LC, Benoit BM, Ubriani R, Vittorio CC, Junkins-Hopkins JM, Wysocka M, Rook AH: Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798–812.

7 Jendrossek V, Handrick R: Membrane targeted anticancer drugs: potent inducers of apoptosis and putative radiosensitisers. Curr Med Chem Anticancer Agents 2003;3:343–353.
8 Ruiter GA, Zerp SF, Bartelink H, van Blitterswijk WJ, Verheij M: Anti-cancer alkyl-lysophospholipids inhibit the phosphatidylinositol 3-kinase-akt/pkb survival pathway. Anticancer Drugs 2003;14:167–173.
9 Dummer R, Krasovec M, Roger J, Sindermann H, Burg G: Topical administration of hexadecylphosphocholine in patients with cutaneous lymphomas: results of a phase I/II study. J Am Acad Dermatol 1993;29:963–970.
10 Dumontet C, Thomas L, Berard F, Gimonet JF, Coiffier B: A phase II trial of miltefosine in patients with cutaneous T-cell lymphoma. Bull Cancer 2006;93:E115–E118.
11 Sigmundsdottir H, Johnston A, Gudjonsson JE, Bjarnason B, Valdimarsson H: Methotrexate markedly reduces the expression of vascular E-selectin, cutaneous lymphocyte-associated antigen and the numbers of mononuclear leucocytes in psoriatic skin. Exp Dermatol 2004;13:426–434.
12 Argyropoulos CL, Lamberg SI, Clendenning WE, Fischmann AB, Jegasothy B, Zackheim H, Peck GL: Preliminary evaluation of 15 chemotherapeutic agents applied topically in the treatment of mycosis fungoides. Cancer Treat Rep 1979;63:619–621.
13 Demierre MF, Vachon L, Ho V, Sutton L, Cato A, Leyland-Jones B: Phase 1/2 pilot study of methotrexate-laurocapram topical gel for the treatment of patients with early-stage mycosis fungoides. Arch Dermatol 2003;139:624–628.
14 Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M: Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600–607.
15 Hengge UR, Benninghoff B, Ruzicka T, Goos M: Topical immunomodulators – progress towards treating inflammation, infection, and cancer. Lancet Infect Dis 2001;1:189–198.
16 Schon MP, Schon M: TLR7 and TLR8 as targets in cancer therapy. Oncogene 2008;27:190–199.
17 Suchin KR, Junkins-Hopkins JM, Rook AH: Treatment of stage IA cutaneous T-cell lymphoma with topical application of the immune response modifier imiquimod. Arch Dermatol 2002;138:1137–1139.
18 Dummer R, Urosevic M, Kempf W, Kazakov D, Burg G: Imiquimod induces complete clearance of a PUVA-resistant plaque in mycosis fungoides. Dermatology 2003;207:116–118.
19 Chong A, Loo WJ, Banney L, Grant JW, Norris PG: Imiquimod 5% cream in the treatment of mycosis fungoides – a pilot study. J Dermatol Treat 2004;15:118–119.
20 Didona B, Benucci R, Amerio P, Canzona F, Rienzo O, Cavalieri R: Primary cutaneous CD30+ T-cell lymphoma responsive to topical imiquimod (Aldara). Br J Dermatol 2004;150:1198–1201.
21 Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL: Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275–280.
22 Ardigo M, Cota C, Berardesca E: Unilesional mycosis fungoides successfully treated with imiquimod. Eur J Dermatol 2006;16:446.
23 Coors EA, Schuler G, von den Driesch P: Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391–393.
24 Chiam LY, Chan YC: Solitary plaque mycosis fungoides on the penis responding to topical imiquimod therapy. Br J Dermatol 2007;156:560–562.
25 Stavrakoglou A, Brown VL, Coutts I: Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620–622.
26 Martinez-Gonzalez MC, Verea-Hernando MM, Yebra-Pimentel MT, Del Pozo J, Mazaira M, Fonseca E: Imiquimod in mycosis fungoides. Eur J Dermatol 2008;18:148–152.
27 Ariffin N, Khorshid M: Treatment of mycosis fungoides with imiquimod 5% cream. Clin Exp Dermatol 2006;31:822–823.
28 Ehst BD, Dreno B, Vonderheid EC: Primary cutaneous CD30+ anaplastic large cell lymphoma responds to imiquimod cream. Eur J Dermatol 2008;18:467–468.
29 Richmond HM, Lozano A, Jones D, Duvic M: Primary cutaneous follicle center lymphoma associated with alopecia areata. Clin Lymphoma Myeloma 2008;8:121–124.
30 Urosevic M, Dummer R, Conrad C, Beyeler M, Laine E, Burg G, Gilliet M: Disease-independent skin recruitment and activation of plasmacytoid predendritic cells following imiquimod treatment. J Natl Cancer Inst 2005;97:1143–1153.
31 Garland SM: Imiquimod. Curr Opin Infect Dis 2003;16:85–89.
32 Owens ML, Bridson WE, Smith SL, Myers JA, Fox TL, Wells TM: Percutaneous penetration of Aldara cream, 5% during the topical treatment of genital and perianal warts. Prim Care Update Ob Gyns 1998;5:151.
33 Dunn GP, Koebel CM, Schreiber RD: Interferons, immunity and cancer immunoediting. Nat Rev Immunol 2006;6:836–848.
34 Kaplan EH, Rosen ST, Norris DB, Roenigk HH Jr, Saks SR, Bunn PA Jr: Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208–212.
35 Jimbow K, Yamana K, Ishida O, Kawamura M, Ito Y, Maeda K: Evaluation of rIFN-gamma in the treatment of lymphoma and melanoma of the skin by systemic and intralesional administration (in Japanese). Gan To Kagaku Ryoho 1987;14:152–158.
36 Dummer R, Hassel JC, Fellenberg F, Eichmuller S, Maier T, Slos P, Acres B, Bleuzen P, Bataille V, Squiban P, Burg G, Urosevic M: Adenovirus-mediated intralesional interferon-gamma gene transfer induces tumor regressions in cutaneous lymphomas. Blood 2004;104:1631–1638.
37 Urosevic M: Drug evaluation: TG-1042, an adenovirus-mediated IFNgamma gene delivery for the intratumoral therapy of primary cutaneous lymphomas. Curr Opin Investig Drugs 2007;8:493–498.
38 Urosevic M, Fujii K, Calmels B, Laine E, Kobert N, Acres B, Dummer R: Type I IFN innate immune response to adenovirus-mediated IFN-gamma gene transfer contributes to the regression of cutaneous lymphomas. J Clin Invest 2007;117:2834–2846.
39 Smith MR: Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003;22:7359–7368.
40 Cartron G, Watier H, Golay J, Solal-Celigny P: From the bench to the bedside: ways to improve rituximab efficacy. Blood 2004;104:2635–2642.
41 Leget GA, Czuczman MS: Use of rituximab, the new FDA-approved antibody. Curr Opin Oncol 1998;10:548–551.
42 McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825–2833.
43 Davis TA, White CA, Grillo-Lopez AJ, Velasquez WS, Link B, Maloney DG, Dillman RO, Williams ME, Mohrbacher A, Weaver R, Dowden S, Levy R: Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. J Clin Oncol 1999;17:1851–1857.
44 Heinzerling L, Dummer R, Kempf W, Schmid MH, Burg G: Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol 2000;136:374–378.
45 Kerl K, Prins C, Saurat JH, French LE: Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. Br J Dermatol 2006;155:1197–1200.
46 Pandolfino TL, Siegel RS, Kuzel TM, Rosen ST, Guitart J: Primary cutaneous B-cell lymphoma: review and current concepts. J Clin Oncol 2000;18:2152–2168.
47 Gaullier JM, Berg K, Peng Q, Anholt H, Selbo PK, Ma LW, Moan J: Use of 5-aminolevulinic acid esters to improve photodynamic therapy on cells in culture. Cancer Res 1997;57:1481–1486.

48 Peng Q, Berg K, Moan J, Kongshaug M, Nesland JM: 5-Aminolevulinic acid-based photodynamic therapy: principles and experimental research. Photochem Photobiol 1997;65:235–251.
49 Boehncke WH, Ruck A, Naumann J, Sterry W, Kaufmann R: Comparison of sensitivity towards photodynamic therapy of cutaneous resident and infiltrating cell types in vitro. Lasers Surg Med 1996;19:451–457.
50 Boehncke WH, Konig K, Ruck A, Kaufmann R, Sterry W: In vitro and in vivo effects of photodynamic therapy in cutaneous T cell lymphoma. Acta Derm Venereol 1994;74: 201–205.
51 Orenstein A, Haik J, Tamir J, Winkler E, Trau H, Malik Z, Kostenich G: Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application. Dermatol Surg 2000;26:765–769, discussion 769–770.
52 Rittenhouse-Diakun K, Van Leengoed H, Morgan J, Hryhorenko E, Paszkiewicz G, Whitaker JE, Oseroff AR: The role of transferrin receptor (CD71) in photodynamic therapy of activated and malignant lymphocytes using the heme precursor delta-aminolevulinic acid (ALA). Photochem Photobiol 1995;61:523–528.
53 Svanberg K, Andersson T, Killander D, Wang I, Stenram U, Andersson-Engels S, Berg R, Johansson J, Svanberg S: Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitization and laser irradiation. Br J Dermatol 1994;130:743–751.
54 Wolf P, Fink-Puches R, Cerroni L, Kerl H: Photodynamic therapy for mycosis fungoides after topical photosensitization with 5-aminolevulinic acid. J Am Acad Dermatol 1994;31:678–680.
55 Ammann R, Hunziker T: Photodynamic therapy for mycosis fungoides after topical photosensitization with 5-aminolevulinic acid. J Am Acad Dermatol 1995;33:541.
56 Stables GI, Stringer MR, Robinson DJ: The treatment of cutaneous T-cell lymphoma by topical aminolaevulinic acid photodynamic therapy. Br J Dermatol 1997;137:50.
57 Eich D, Eich HT, Otte HG, Ghilescu V, Stadler R: Photodynamic therapy of cutaneous T-cell lymphoma at special sites (in German). Hautarzt 1999;50:109–114.
58 Wang I, Bauer B, Andersson-Engels S, Svanberg S, Svanberg K: Photodynamic therapy utilising topical delta-aminolevulinic acid in non-melanoma skin malignancies of the eyelid and the periocular skin. Acta Ophthalmol Scand 1999;77:182–188.
59 Edstrom DW, Porwit A, Ros AM: Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: clinical and histological response. Acta Derm Venereol 2001;81:184–188.
60 Edstrom DW, Hedblad MA: Long-term follow-up of photodynamic therapy for mycosis fungoides. Acta Derm Venereol 2008;88: 288–290.
61 Markham T, Sheahan K, Collins P: Topical 5-aminolaevulinic acid photodynamic therapy for tumour-stage mycosis fungoides. Br J Dermatol 2001;144:1262–1263.
62 Leman JA, Dick DC, Morton CA: Topical 5-ALA photodynamic therapy for the treatment of cutaneous T-cell lymphoma. Clin Exp Dermatol 2002;27:516–518.
63 Paech V, Lorenzen T, Stoehr A, Lange K, Merz H, Meigel WN, Plettenberg A: Remission of a cutaneous mycosis fungoides after topical 5-ALA sensitisation and photodynamic therapy in a patient with advanced HIV-infection. Eur J Med Res 2002;7:477–479.
64 Umegaki N, Moritsugu R, Katoh S, Harada K, Nakano H, Tamai K, Hanada K, Tanaka M: Photodynamic therapy may be useful in debulking cutaneous lymphoma prior to radiotherapy. Clin Exp Dermatol 2004;29:42–45.
65 Coors EA, von den Driesch P: Topical photodynamic therapy for patients with therapy-resistant lesions of cutaneous T-cell lymphoma. J Am Acad Dermatol 2004;50:363–367.
66 Zane C, Venturini M, Sala R, Calzavara-Pinton P: Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. Photodermatol Photoimmunol Photomed 2006;22:254–258.
67 Hegyi J, Frey T, Arenberger P: Unilesional mycosis fungoides treated with photodynamic therapy: a case report. Acta Dermatovenereol Alp Panonica Adriat 2008;17:75–78.
68 Recio ED, Zambrano B, Alonso ML, de Eusebio E, Martin M, Cuevas J, Jaen P: Topical 5-aminolevulinic acid photodynamic therapy for the treatment of unilesional mycosis fungoides: a report of two cases and review of the literature. Int J Dermatol 2008;47:410–413.
69 Mori M, Campolmi P, Mavilia L, Rossi R, Cappugi P, Pimpinelli N: Topical photodynamic therapy for primary cutaneous B-cell lymphoma: a pilot study. J Am Acad Dermatol 2006;54:524–526.
70 Bonis B, Kemeny L, Dobozy A, Bor Z, Szabo G, Ignacz F: 308 nm UVB excimer laser for psoriasis. Lancet 1997;350:1522.
71 Novak Z, Bonis B, Baltas E, Ocsovszki I, Ignacz F, Dobozy A, Kemeny L: Xenon chloride ultraviolet B laser is more effective in treating psoriasis and in inducing T cell apoptosis than narrow-band ultraviolet B. J Photochem Photobiol B 2002;67:32–38.
72 Novak Z, Berces A, Ronto G, Pallinger E, Dobozy A, Kemeny L: Efficacy of different UV-emitting light sources in the induction of T-cell apoptosis. Photochem Photobiol 2004;79:434–439.
73 Nistico S, Costanzo A, Saraceno R, Chimenti S: Efficacy of monochromatic excimer laser radiation (308 nm) in the treatment of early stage mycosis fungoides. Br J Dermatol 2004;151:877–879.
74 Passeron T, Zakaria W, Ostovari N, Perrin C, Larrouy JC, Lacour JP, Ortonne JP: Efficacy of the 308-nm excimer laser in the treatment of mycosis fungoides. Arch Dermatol 2004; 140:1291–1293.
75 Passeron T, Angeli K, Cardot-Leccia N, Perrin C, Lacour JP, Ortonne JP: Treatment of mycosis fungoides by 308 nm excimer laser: a clinical and histological study in 10 patients (in French). Ann Dermatol Vénéréol 2007;134:225–231.
76 Kontos AP, Kerr HA, Malick F, Fivenson DP, Lim HW, Wong HK: 308-nm excimer laser for the treatment of lymphomatoid papulosis and stage IA mycosis fungoides. Photodermatol Photoimmunol Photomed 2006;22: 168–171.
77 Meisenheimer JL: Novel use of 308-nm excimer laser to treat a primary cutaneous CD30+ lymphoproliferative nodule. J Drugs Dermatol 2007;6:440–442.
78 Knobler E: Current management strategies for cutaneous T-cell lymphoma. Clin Dermatol 2004;22:197–208.
79 Wong TW, Zhao YL, Sen A, Hui SW: Pilot study of topical delivery of methotrexate by electroporation. Br J Dermatol 2005;152: 524–530.
80 Lee WR, Shen SC, Fang CL, Zhuo RZ, Fang JY: Topical delivery of methotrexate via skin pretreated with physical enhancement techniques: low-fluence erbium:YAG laser and electroporation. Lasers Surg Med 2008;40: 468–476.
81 Moarbess G, El-Hajj H, Kfoury Y, El-Sabban ME, Lepelletier Y, Hermine O, Deleuze-Masquefa C, Bonnet PA, Bazarbachi A: EAPB0203, a member of the imidazoquinoxaline family, inhibits growth and induces caspase-dependent apoptosis in T-cell lymphomas and HTLV-I-associated adult T-cell leukemia/lymphoma. Blood 2008;111:3770–3777.
82 Shohat M, Hodak E, Sredni B, Shohat B, Sredni D, David M: Cytokine profile of patients with mycosis fungoides and the immunomodulatory effect of AS101. Acta Derm Venereol 2001;81:255–257.
83 Frei GM, Kremer M, Hanschmann KM, Krause S, Albeck M, Sredni B, Schnierle BS: Antitumour effects in mycosis fungoides of the immunomodulatory, tellurium-based compound, AS101. Br J Dermatol 2008;158: 578–586.
84 Kim Y, Girardi M, McAuley S, Schmalbach T: Cutaneous T-cell lymphoma (CTCL) responses to a TLR9 agonist CpG immunomodulator (CpG 7909), a phase I study. 2004 ASCO Annual Meeting Proceedings (post-meeting edition). J Clin Oncol 2004;22(No 14S, supplement):6600.

85 Leonard JP, Link BK, Emmanouilides C, Gregory SA, Weisdorf D, Andrey J, Hainsworth J, Sparano JA, Tsai DE, Horning S, Krieg AM, Weiner GJ: Phase I trial of Toll-like receptor 9 agonist PF-3512676 with and following rituximab in patients with recurrent indolent and aggressive non-Hodgkin's lymphoma. Clin Cancer Res 2007;13:6168–6174.
86 Fernandez-Guarino M, Garcia-Morales I, Harto A, Montull C, Perez-Garcia B, Jaen P: Photodynamic therapy: new indications (in Spanish). Actas Dermosifiliogr 2007;98:377–395.
87 Akita Y, Watanabe D, Yanagishita T, Kuhara T, Kawamura C, Masuda Y, Kawada M, Nakaseko H, Tamada Y, Matsumoto Y: The effect of psoralen plus ultraviolet A in vitro in HUT-78 enhances by 5-aminolevulinic acid. Photodermatol Photoimmunol Photomed 2007;23:95–97.
88 Farkas A, Kemeny L: Applications of the 308-nm excimer laser in dermatology. Laser Physics 2006;16:876–883.
89 Chen GQ, Zhu J, Shi XG, Ni JH, Zhong HJ, Si GY, Jin XL, Tang W, Li XS, Xong SM, Shen ZX, Sun GL, Ma J, Zhang P, Zhang TD, Gazin C, Naoe T, Chen SJ, Wang ZY, Chen Z: In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia: As_2O_3 induces NB4 cell apoptosis with downregulation of BCL-2 expression and modulation of PML-RAR alpha/PML proteins. Blood 1996;88:1052–1061.
90 Soignet SL, Maslak P, Wang ZG, Jhanwar S, Calleja E, Dardashti LJ, Corso D, DeBlasio A, Gabrilove J, Scheinberg DA, Pandolfi PP, Warrell RP Jr: Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339:1341–1348.
91 Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, Zhu J, Tang W, Sun GL, Yang KQ, Chen Y, Zhou L, Fang ZW, Wang YT, Ma J, Zhang P, Zhang TD, Chen SJ, Chen Z, Wang ZY: Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL). II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 1997;89:3354–3360.
92 Michel L, Dupuy A, Jean-Louis F, Sors A, Poupon J, Viguier M, Musette P, Dubertret L, Degos L, Dombret H, Bachelez H: Arsenic trioxide induces apoptosis of cutaneous T cell lymphoma cells: evidence for a partially caspase-independent pathway and potentiation by ascorbic acid (vitamin C). J Invest Dermatol 2003;121:881–893.
93 Tun-Kyi A, Qin JZ, Oberholzer PA, Navarini AA, Hassel JC, Dummer R, Dobbeling U: Arsenic trioxide down-regulates antiapoptotic genes and induces cell death in mycosis fungoides tumors in a mouse model. Ann Oncol 2008;19:1488–1494.